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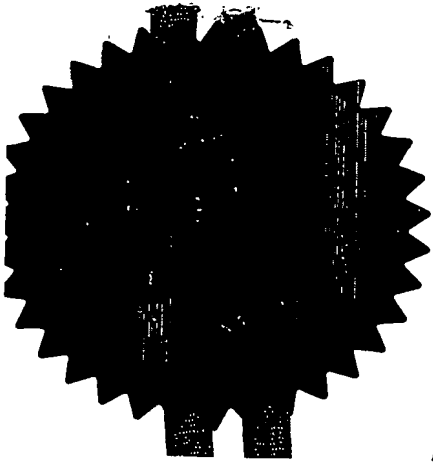
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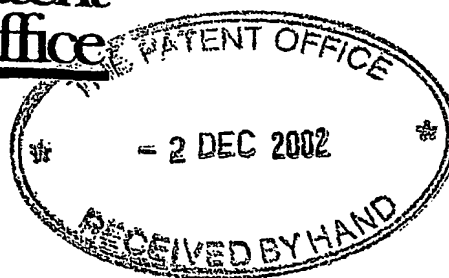
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Signed *Andrew Gasey*
Dated 19 December 2003



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1. Your reference

45429.gb01/HRW

2. Patent application number

(The Patent Office will fill in this part)

0228079.0

03DEC02 E767953-1 001631

P01/7700 0.00-0228079.0

02 DEC 2002

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Laxdale Limited
Kings Park House
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Stirling FK7 9JQ
Scotland

Patents ADP number (if you know it)

If the applicant is a corporate body, give the

England & Wales

03DEC02 E767953-1 001631

4. Title of the invention

Huntington's Disease

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
16 Theobalds Road
LONDON
WC1X 8PL

Patents ADP number (if you know it)

91001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application
(if you know it)

Date of filing
(day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

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(day/month/year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

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See note (d))

yes

Patents Form 1/77

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Continuation sheets of this form 0

Description 6

Claim(s) 2

Abstract 0

Drawing(s) 0



10. If you are also filing any of the following, state how many against each item.

Priority documents -

Translations of priority documents -

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*) -

Request for preliminary examination and search (*Patents Form 9/77*) -

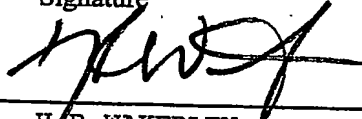
Request for substantive examination (*Patents Form 10/77*) -

Any other documents (please specify)

11:

I/We request the grant of a patent on the basis of this application.

Signature



Date

~~29 November 2002~~

2 December 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

H/R WAKERLEY
020-7242 0901

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HUNTINGTON'S DISEASE

Huntington's Disease (HD) is a lethal genetic disease caused by mutations in the gene for the protein Huntingtin on human chromosome 4. The fatty acid, eicosapentaenoic acid (EPA), in any appropriate pharmaceutical form can be used to treat HD (European patent application 1148873).

The present invention relates to the treatment of HD and is based on a finding that the therapeutic effect of EPA occurs particularly in those patients with a particular genetic form of HD.

The present invention provides a method of identifying patients with HD, or individuals who are at risk of developing HD, who are particularly likely to respond to treatment with EPA in any appropriate form and comprises the step of carrying out a test to determine the number of CAG repeats in the Huntingtin gene and identifying those subjects with 45 or fewer repeats.

If the subject has less than 36 repeats, this is an indication of a normal individual. In a preferred test, the subjects selected are those with 44 or fewer, or between 36 and 44, CAG repeats.

The test may be carried out on a sample taken from the subject for analysis purposes only.

The present invention further provides a method of treating HD, and a method for preventing the development of symptoms in individuals who are at risk of developing HD, comprising the step of determining the number of CAG repeats in the subject's gene for Huntingtin and, if this is 45 or fewer, administering to the subject EPA in any bioavailable form. In a preferred test, the subjects selected for administration of EPA are those with 44 or fewer, or between 36 and 44, CAG repeats.

The EPA used in the methods of the present invention is preferably ethyl-EPA.

A CAG repeat number of 46 or more does not show any difference at all on treatment between administration of a placebo and of EPA. In contrast, and unexpectedly, patients suffering from HD who have CAG repeat numbers of 45 or below show a large benefit on administration of EPA.

Although all HD patients have a genetic abnormality in the same gene, not all patients have the same abnormality. The normal gene for huntingtin contains a sequence of CAG repeats which code for a polyglutamine sequence in the gene itself. Even in normal individuals, the polyglutamine sequence is of variable length, but so long as it contains less than 36 CAG repeats and hence less than 36 glutamines in the polyglutamine sequence, the individual will be normal. However, when the sequence contains 36 or

more CAG repeats and consequent glutamine sequences, HD will develop. Patients with HD may have anything from 36 to more than 100 CAG repeats.

HD usually starts with movement disorders, particularly affecting the face, head and neck and limbs. These progress and are often accompanied by psychiatric abnormalities and cognitive impairment leading to dementia. The abnormalities are initially caused by huntingtin damage to the neurons of the striatum, but later wide areas of the brain may be involved. Eventually patients become bedridden and completely unable to care for themselves. They usually die 10 to 25 years after the onset of the disease.

The number of CAG repeats has a strong effect on the age of onset of the disease. Patients with numbers only just over 35 may not become ill until their 50s or 60s or even later. Patients with repeat numbers over 60 may become ill in adolescence or even in childhood. Most patients, however, tend to fall ill between the ages of 30 and 50. Once the disease has started, there is a tendency for patients with large numbers of CAG repeats to progress more rapidly although this effect is weak compared to the strong effect on age of onset.

The number of CAG repeats can be identified by diagnostic tests based on the polymerase chain reaction (PCR). These tests provide a firm diagnosis

of HD and can, of course, be applied to pre-symptomatic patients. However, relatively few pre-symptomatic individuals who are at risk of being carriers of the HD gene, and therefore who will inevitably develop the disease at some time, bother to get tested. Many people who do have HD symptoms also do not get tested. The main argument for not being tested is that there are no treatments available for HD, so what is the point of knowing exactly that the gene is present and what sort of gene it is.

Clinical trials of the ethyl ester of eicosapentaenoate (ethyl-EPA) in HD have provided strong evidence of the benefit of EPA in HD, and also, completely unexpectedly, of the value of CAG genetic testing.

135 patients with genetically-confirmed HD were entered into a one year trial. They were randomised to receive either 2g/day of ethyl-EPA or an identical-appearing placebo. They were evaluated at baseline, six months and 12 months on the total motor score (TMS) subscale of the Unified Huntington's Disease Rating Scale (UHDRS). The UHDRS is the standard rating scale which is used to monitor the development of HD. The TMS is the component of the UHDRS which changes most reliably, rapidly and consistently and is therefore appropriate for monitoring the outcome of clinical trials.

At the end of one year, change in TMS was compared in the placebo group and the ethyl-EPA group. Overall there was a better outcome on ethyl-EPA than on placebo but this was not statistically significant. However, when patients were stratified on the basis of their CAG repeat numbers, a dramatic benefit of ethyl-EPA was uncovered. Patients who had CAG repeat number of 46 or more did not show any difference at all between placebo and ethyl-EPA. In contrast, patients who had CAG repeat numbers of below 45 showed a large benefit from ethyl-EPA. Placebo patients with CAG repeat numbers below 45 deteriorated by an average of 5.3%. In contrast, the same group of patients on ethyl-EPA improved over the year by 19.3%. This difference was highly statistically significant on either analysis of covariance or on chi square testing. Particularly striking is the fact that the great majority of patients on ethyl-EPA actually improved. Previously the best that had been hoped for in neurodegenerative diseases like HD was a slowing of deterioration rather than any actual improvement. Since the ethyl-EPA group improved more than three and a half times more than the patients on placebo over one year, this means that after one year the EPA and placebo patients had separated by more than four and a half years of disease progression. Putting it another way, the treated patients had gained at least four and a half years of useful life. In contrast, the patients who had 46 or more CAG repeats did not show

any difference between the ethyl-EPA and placebo treatment.

Claims

1. A method of identifying patients with Huntington's disease, or individuals who are at risk of developing Huntington's disease, who will respond to treatment with EPA in any bioavailable form comprising the step of determining the number of CAG repeats in the huntingtin gene and identifying those subjects with 45 or fewer repeats.
2. A method according to claim 1, in which the treatment comprises administration of ethyl-EPA.
3. A method of treating Huntington's disease comprising the steps of identifying patients having 45 or fewer CAG repeats in the gene for huntingtin and administering to those patients EPA in any bioavailable form.
4. A method of preventing the development of symptoms in individuals who are at risk of developing Huntington's disease comprising the steps of identifying individuals having 45 or fewer CAG repeats in the gene for huntingtin and administering to those individuals EPA in any bioavailable form.

5. A method according to claim 3 or 4 in which the EPA administered is in the form of ethyl-EPA.